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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,835	01/11/2001	Gabriele Multhoff	105032-991230	1173

7590 11/03/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,835	MULTHOFF, GABRIELE	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *31-43,45-56 and 58-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *31-43,45-56 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 42, 50 and 55 have been amended. Because claim 43 is not rejected by the prior art the election of species requirement of the Paper mailed Aug 5, 2002 is withdrawn and claim 49 will be included with the claims under consideration. Claims 31-43, 45-56, and 58-60 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claim 31 is objected to for the lack of a conjugation between the words "fragment" and "polypeptide" in line 6. For purpose of examination, the claim will be read as "fragment or polypeptide".

4. Claim 42 is objected to for the typographical error in line 5 of section ii which recites "polypeptide having 705 of greater homology" rather than "polypeptide having 70% or greater homology.

5. The rejection of claims 45-47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record..

The recitation of "said administering" in claim 45 lacks antecedent basis in claim 31. Claim 45 is ultimately dependent upon claim 31 which directs the contacting of NK cells with the Hsp70 protein, but does not recite administering the Hsp70 protein to said cells.

6. Claims 31-43, 45-56 and 58-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites "an isolated C-terminal fragment of Hsp70, wherein said fragment is selected from the group consisting of amino acids 384-641 of SEQ ID NO:1, an isolated polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1". Firstly,

this is an improper Markush group, which should be constructed to read: selected from the group consisting of A and B; secondly, it is unclear how a peptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1 can be included in a Markush group defining the metes and bounds of C-terminal fragment of hsp70, because a polypeptide having at least 70% homology to amino acids 384-641 of SEQ ID NO:1 would encompass a much larger scope of polypeptides than the C-terminal fragment of hsp70.

Claim 42, 50 and 55 recite "an isolated C-terminal fragment of Hsp70, wherein said fragment is selected from the group consisting of amino acids 384-641 of SEQ ID NO:1, an isolated polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1, derivatives thereof, a polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1 and derivatives thereof". Firstly, "derivatives thereof" is listed twice as an element of the Markush group; secondly it is unclear how a peptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1 or a "derivative" can be included in a Markush group defining the metes and bounds of C-terminal fragment of hsp70, because a polypeptide having at least 70% homology to amino acids 384-641 of SEQ ID NO:1 or derivatives of amino acids 384-641 would encompass a much larger scope of polypeptides and chemically modified polypeptide than the C-terminal fragment of hsp70.

Claims 42, 50 and 55 are vague and indefinite because it is unclear if an increase in cytolytic activity of the NK cells or proliferation of the NK cells is a limitation to be applied to "derivatives" because the term "derivatives" was omitted from the limitations required by "isolated proteins, fragment or polypeptide"

7. The rejection of claims 42, 43, 48, 50-53, 55, 56 and 58-60 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

(A) As drawn to inadequate written description of a genus

Claims 50-53 are drawn in part to a genus comprising derivatives of proteins comprising the amino acid sequence of residues 386-641 of SEQ ID NO:1 and derivatives of polypeptide having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1. Claims 42,

43, 45-48, 55, 56 and 58-60 are drawn in part to method claims for the in vivo activation of the "immune system" in a patients comprising the administration of proteins comprising derivatives of proteins comprising the amino acid sequence of residues 386-641 of SEQ ID NO:1 and derivatives of polypeptide having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1. The specification sets forth Hsp70 as SEQ ID NO:1, and teaches that residues 384-641 of SEQ ID NO:1 are responsible for the activation of NK cells into cytotoxic cells. The specification teaches that the Hsp70 protein is a heat shock protein which is differentially expressed on many types of cancerous cells. The specification contemplates methods of activating NK cells by means of proteins having at least 70% homology to amino acid residues 384-681 of SEQ ID NO:1, wherein contacting of NK cells with an uncomplexed fragment of amino acid residues 384-641 of SEQ ID NO:1 stimulates the proliferation of NK cells and increases the cytolytic activity of NK cells. The method of claims 42, 43, 45-48, 55, 56 and 58-60 or the products of claims 50-53 are not limited to the direct increase in cytolytic activity of NK cells or the increase in proliferation of NK cells by contact with the derivatives of proteins comprising the amino acid sequence of residues 386-641 of SEQ ID NO:1 and derivatives of polypeptide having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1. Thus, the genus of proteins encompassed by the method claims and product claims is highly variant because the derivatives of proteins comprising the amino acid sequence of residues 386-641 of SEQ ID NO:1 and derivatives of polypeptide having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1 are not confined to proteins which directly activate NK cells. Further, the specification lacks a limiting definition for the structural requirements of a "derivative" which could serve to limit the structural attributes of the genus of derivatives The proteins encompassed by the claims could serve to activate dendritic cells or B cells or T cells, all of which would satisfy the specific limitation of activating the "immune response". Thus, when given the broadest reasonable interpretation, the genus of derivatives of amino acids residues 384-641 of SEQ ID NO:1 and derivatives of polypeptide having at least 70% homology to amino acid residues 384-641 of SEQ ID NO:1 encompassing widely ranging structural deviations from Hsp70 and the amino acid sequence comprising residues 384-681 of SEQ ID NO:1, wherein said deviations could include fusions with any other amino acid sequence, alterations of the protein backbone, coupling with any known chemical which reacts with amino

acid sequences, proteolytic fragments of the amino acid sequence comprising residues 384-641 of SEQ ID NO:1, enzymatic modification of said amino acid sequence, and amino acid substitutions, deletions and additions to residues 381-641 of SEQ ID NO:1. The disclosure of SEQ ID NO:1 is inadequate written description for this multitude of species having structural and functional limitations which differ from that of amino acid residues 381-641 of SEQ ID NO:1.

(B)As drawn to new matter

Claims 42, 43, 48, 50-56 and 58-60. The instant method claims, 42, 43, 48, 55, 56 and 58-60 are drawn in part to a method reliant on derivatives of a polypeptide having at least 70% sequence homology to amino acids 384-641 of SEQ ID NO:1. The instant product claims, 50-53, are drawn in part to derivatives of a polypeptide having at least 70% sequence homology to amino acids 384-641 of SEQ ID NO:1.

The specification states on page 2, lines 22-26 that the invention relates to a Hsp70 protein, a carboxyl terminal fragment of a Hsp70 protein or a derivative thereof or a protein having 70% sequence homology to the C-terminal region of the Hsp70 protein. This does not provide support for claims drawn to derivative of a protein having 70% sequence homology to the C-terminal region of the Hso70 protein.

8. Claims 31-43, 45-56, and 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods reliant upon a polypeptide fragment comprising amino acid residues 341-641 of SEQ ID NO:1, wherein said polypeptide induces an immune response by NK cells, does not reasonably provide enablement for methods reliant upon a polypeptide having 70% or greater homology, to amino acids 384-641 of SEQ ID NO:1, wherein said polypeptide induces an immune response by NK cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The instant method claims 31-43, 45-49, 55, 56 and 58-60 are drawn in part to a method reliant on the identity of a polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1, wherein said polypeptide induces an immune response by NK cells, wherein said response increases cytolytic activity of the NK cells or stimulates proliferation of the NK

cells. The instant product claims are drawn in part to polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1, wherein said polypeptide induces an immune response by NK cells, wherein said response increases cytolytic activity of the NK cells or stimulates proliferation of the NK cells. Claim 54 is drawn to NK cells which are activated by the method of claim 31 and thus are dependent in part upon the polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO:1, wherein said polypeptide induces an immune response by NK cells. The specification does not teach how to make the broadly claimed variant polypeptides which would have the required functional activities of activating the cytolytic or proliferative activity of NK cells. The art teaches that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al. (J of Cell Bio. 111:2129-2138, 1990), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein.. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a protein that shares only 70% homology with SEQ ID NO: 1 would will function as suggested. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use polypeptides comprising variant C-terminus fragments of SEQ ID NO:1 which will have the ability to activiate NK cells. The specification provides no evidence that a polypeptide having as little as 70% sequence identity with residues 384-641 of SEQ ID NO:1 would function as claimed, and the teachings of the art indicate the ability to make polypeptide variants which maintain the functional attributes of the parent polypeptide is unreliable. Thus, given the lack of teachings in the specification as to how to make the claimed variants, and the lack of a single example which would demonstrate that a polypeptide sequence having as little as 70% sequence homology with residues 384-641 of SEQ ID NO:1 would function to increase the cytolytic and proliferative activity of NK cells, one of

skill in the art would be subject to undue experimentation in order to make the broadly claimed polypeptides and in order to use the broadly claimed methods.

9. The rejection of claims 50-53under 35 U.S.C. 102(b) as being anticipated by Jindal et al (Bio/Technology, 1995, vol. 13, pp. 1105-1109) is maintained for reasons of record.

Jindal et al discloses isolated, purified recombinant human Hsp70 eluted by a NaCl solution from a Superdex 200 column equilibrated with HEPES (page 1108, second column, under the heading "Size Exclusion Chromatography"). Both HEPES and NaCl are pharmaceutically acceptable diluents.

Applicant argues that Jindal et al does not disclose a pharmaceutical composition and asserts that the polypeptide of Jindal et al in NaCl or HEPES buffer is not a pharmaceutical composition. This has been considered but not found persuasive. Both NaCl and HEPES as buffer which are used for the introduction of a protein in vivo. The Hsp70 protein of Jindal et al is identical to the instant Hsp70 protein. Applicant has further amended the product claims to specify that the Hsp70 protein increases the cytolytic and proliferative function of NK cells. However, the recited limitations would be inherent in the Hsp70 protein of Jindal et al which is identical to that of the claimed Hsp70 protein.

10. All other rejections and objections as set forth in the previous Office action are withdrawn.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/30/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER